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Incidence of complications of peptic ulcers in patients with *Helicobacter pylori* (Hp) infection and/or NSAID use in the era of Hp eradication

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Hp and NSAID are considered as major pathogens in peptic ulcerations and their complications but little is known about the incidence of ulcers and their complications following widespread use of Hp eradication. The aims of the study were: 1) to analyze incidence of ulcers and their complications, bleeding and perforations at time when the Hp eradication has been used in ulcer therapy, and 2) to assess the impact of Hp infection and NSAID use on the incidence of ulcers and complications.

Material/Methods: From 1996 to 2001, 381 patients with complications of peptic ulcers were admitted to the emergency surgery, including 273 patients with bleeding ulcers and 108 with perforations out of a sample of 6515 dyspeptic patients examined with upper endoscopy and ^{13}C-urea breath test (UBT).

Results: The rate of ulcer bleeding and perforations, remained relatively constant throughout the study period. NSAID use in that group increased form 15.8% in 1999 to 19.4% in 2001. The incidence of Hp in patients with complications assessed by UBT or CLO was 76.7%, while the incidence of Hp in 7920 patients ranged form 72.8% in 1996 to 53.8% in 2001. There were 1940 (29.7%) patients with duodenal and/or gastric ulcer diagnosed by upper gastroscopy. The decline in the prevalence of peptic ulcer from about 44% to 8% occurred over the same time. A slight increase in the number of ulcer resulting from NSAID use was observed so was the number of ulcers without Hp or NSAID (idiopathic).

Conclusions: Despite decreased Hp prevalence, the incidence of ulcers complications remained unchanged probably due to increased use of NSAID and the appearance of idiopathic ulcers.

key words: ***Helicobacter pylori*** • **non-steroidal anti-inflammatory drugs** • **gastric hemorrhage** • **perforation** • **idiopathic ulcers**

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BACKGROUND

Peptic ulcer hemorrhage and perforation remain important emergency situations. Although the crucial role of *H. pylori* infection in the pathogenesis of ulcer has been generally accepted [1,2], its association with ulcer complications is less clear. A strong argument for the etiological role of *H. pylori* in ulcerogenesis is the fact that eradication of this germ prevents the ulcer recurrence but it is less clear whether this therapy also decreases the ulcer complications such as hemorrhage and perforation [3–9]. Despite the marked progress over last 20 years in diagnosis and treatment of ulcer patients, especially the widespread use of the Hp eradication therapy, the mortality rate caused by hemorrhage and perforation worldwide is relatively stable and averages, respectively about 10 and 7% [3–5].

The gross upper gastrointestinal bleeding is the most common complication of peptic ulcer disease. Growing awareness of the role of *H. pylori* infection in the etiopathology of upper gastrointestinal diseases resulted in the major change in the treatment regimens and the widespread use of its eradication also during the emergency bleeding [10].

NSAID, similarly to *H. pylori*, also may cause damage to the gastric mucosa and peptic ulcers. These ulcerogens independently and significantly increase the risk of peptic ulcer and ulcer bleeding. *H. pylori* infection and NSAID seem to cause the majority of bleeding ulcers from gastrointestinal tract. Much controversy, however, surrounds the interaction of *H. pylori* infection and use of NSAID on gastro-duodenal mucosa [10–14]. The severity of dyspeptic symptoms appears worse in infected drug users [14]. More ulcers were found in *H. pylori* positive than *H. pylori* negative users of NSAID [12]. The complex interaction between *H. pylori* and NSAID implies that it is over simplistic to conclude that their relationship is independent, synergistic or antagonistic without considering the influence of other factors [13] such as previous exposure to NSAID, a history of ulcer complication, concurrent use of acid-suppressant therapy, and the difference between gastrotoxicity of various types of NSAID. Current evidence suggests that *H. pylori* may contribute to an increased risk of ulcer development and its bleeding in patients who are about to start NSAID treatment [14], whereas NSAID probably account for the majority of ulcer disease in patients who are already taking long-term NSAID [12]. Based on the meta-analysis of numerous clinical trials, it has been concluded that eradication of *H. pylori* infection reduces the risk of ulcers for patients starting long-term NSAID treatment [12].

The aim of this study was an attempt to analyze the incidence of complications of peptic ulcer disease such as hemorrhage and perforation, in the years 1996–2001 in large samples of dyspeptic patients who consecutively appeared in our *H. pylori* University Center for diagnosis and treatment of dyspeptic symptoms. The question has been risen how these two ulcerogens – the *H. pylori* and the NSAID have influenced the incidence of complications of peptic ulcer disease.

MATERIAL AND METHODS

Analysis of emergency admissions for complication of peptic ulcer was carried out in the 2nd Department of Surgery, College of Medicine of Jagiellonian University, Cracow between 1996 and 2001. Endoscopic and intraoperative findings were analyzed and data from patient history with special attention to NSAID use were reviewed. The prevalence of *H. pylori* infection among in patients with bleeding was assessed by capsulated mini-dose ^{13}C-urea breath test (UBT), while in those with perforation, a biopsy sample of antral mucosa was taken during open or laparoscopic surgery by rapid urease test using CLO test (Delta West Pty Ltd, Bentley, Australia).

Concomitantly the data of the Institute of Physiology, Collegium Medicum of Jagiellonian University, Cracow, where UBT is routinely performed, were analyzed as described before [15]. Among all dyspeptic patients from that group incidence of peptic ulcer disease and use of NSAID were assessed.

During study period, 381 patients with complications of peptic ulcers were admitted to our Department of Surgery and this encompasses 273 patients with bleeding ulcer and 108 patients with perforated ulcer. In the same period, 7920 patients with dyspeptic symptoms were subjected to UBT. No side-effects following the upper endoscopy or swallowing the capsule with ^{13}C-urea (38 mg/capsule) were recorded in our patients with ulcer complication or in controls without complications. Out of these dyspeptic patients, 6515 were subjected to upper endoscopy and most of patients with ulcer complications originated from the dyspeptic patients with gastro-duodenal ulcerations. The study was approved by the Jagiellonian University Ethical Research Committee (KE/99/02/B/271).

RESULTS

The ratio of women to men was like 1:2 in patients with bleeding gastric ulcer patients and this was similar to that in non-bleeding gastric ulcer and in healthy controls.

The rate of complications of peptic ulcer, namely bleeding and perforations, remained relatively constant throughout the 6 yr study period (Fig. 1).

The reported rate of NSAID use in that group increased form 15.8% in 1999 to 19.4% in 2001 yr. The *H. pylori* prevalence in patients with complications of peptic ulcer assessed by UBT or CLO test was 76.7% and this was not significantly different from that detected in non-bleeding gastric ulcer patients (75%) but significantly higher than that in control healthy subjects (60%).

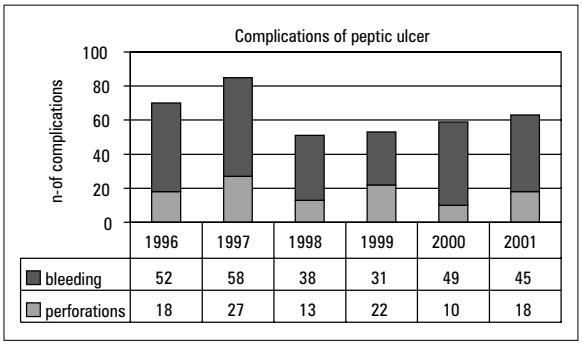

Figure 1. Emergency admissions for complications of peptic ulcer (1999–2001).

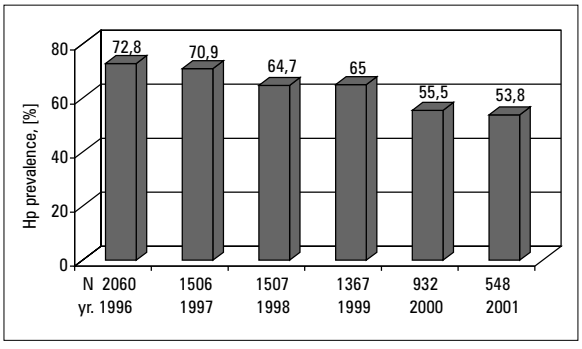

Figure 2. Prevalence of *H. pylori* infection detected by UBT in dyspeptic patients (1996–2001). N = 7920

In 7920 of dyspeptic patients that underwent UBT the incidence of *H. pylori* infection decreased from 72.8% in 1996 to 53.8% in 2001 (Fig. 2). Among 6515 of dyspeptic patients who were submitted to upper endoscopy there were 1940 (29.7%) patients with gastric ulcer and/or duodenal ulcers. A significant decline in the prevalence of peptic ulcer was noted from 43.7% at 1996 to only 7.7% at 2001 yr. At the same period a slight increase in the number of ulcers resulting from the NSAIDs use was observed (from 2.2% to 4.1%). The number of ulcers without *H. pylori* and NSAID (idiopathic ulcers) also increased especially at 2000 and 2001 yr so the ratio of idiopathic ulcers to total number of ulcers significantly increased during this period (Fig. 3).

DISCUSSION

This study demonstrates that during last 6 years the *H. pylori* prevalence detected by UBT in Polish population shows significant decrease from nearly 73% at 1996 to 54% at 2001. Similarly the percent of dyspeptic patients with peptic ulcerations also showed remarkable decline from 43.7% at 1996 to only 7.7% in 2001. At the same time, the ratio of non-*H. pylori*, non-NSAID or idiopathic ulcers increased from about 20% at 1996 to about 30% in 2000-2001.

The significant fall in *H. pylori* prevalence in our population is closely and probably causally correlated with the decline in the occurrence of peptic ulcerations [13] possibly due to the improvement of living standards and widespread use of eradication of *H. pylori* in the treatment of peptic ulcerations.

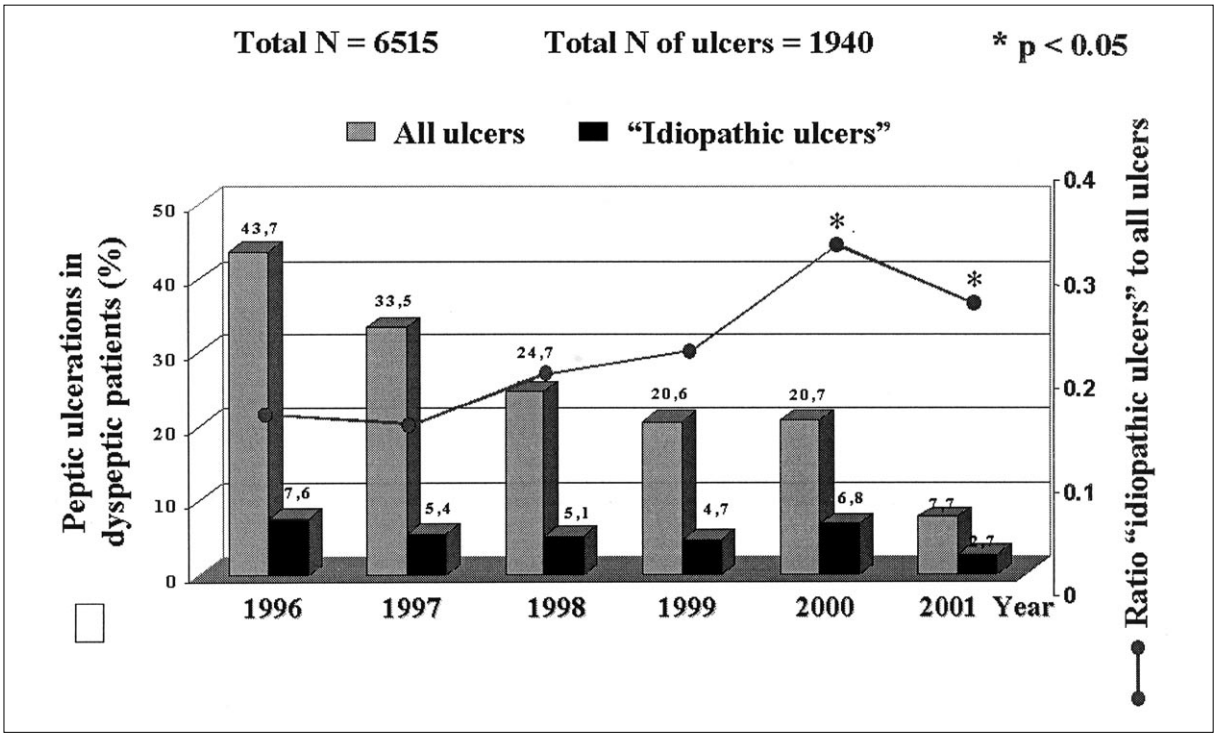

Figure 3. Occurrence of gastroduodenal ulcers in dyspeptic patients with endoscopy (1996–2001). Total N = 6515, total number of ulcers =1940.

The major finding of this report is that despite the decline in the *H. pylori* prevalence in our society and the remarkable decline in the occurrence of peptic ulcerations during last 6 years, the rate of ulcer complications such as hemorrhages and perforations recorded in the emergency surgery, serving for the south part of Poland, was virtually unchanged during the same time. One of the possible reasons for the sustained rate of upper gastrointestinal bleeding could be an increased use of NSAID available in this country without prescription and sold under various names without warning of the possible side-effects. Another explanation for the relatively high incidence of ulcer complications is that they may concern mostly non-*H. pylori*, non-NSAID ulcers (idiopathic), whose rate was found in this study to increase during last 6 years. Similar rise in the rate of idiopathic ulcerations was recently reported by Xia et al. [16] showing that about 14% among 1153 duodenal ulcer patients had this type of ulcerations. Such ulcers may represent serious problem due to ulcer complications such as bleeding or perforation despite the lack of *H. pylori* infection and NSAID use. Further studies are needed to establish whether these idiopathic ulcerations tend to be accompanied by increased rate of complications such as hemorrhage or perforation.

The results of this study are at variance with the recent report of Huang et al [12] based on meta-analysis of 16 multicenter trials showing that; 1) the *H. pylori* infection acts synergistically with NSAID in promoting gastro-duodenal ulcerations, and 2) that peptic ulcers do not develop in patients without *H. pylori* infection or NSAID use. Our finding that relatively large proportion of ulcer patients were neither infected with *H. pylori* nor used NSAID militates against the notion of Huang et al. [12] and the reason for this discrepancy is not known. Furthermore, according to our results based on relatively large sample of ulcer patients (about 6000 patients) examined in one unit in Poland, the *H. pylori* infection actually reduced the risk of NSAID-induced gastro-duodenal ulcerations [13].

CONCLUSIONS

In summary, this study provides first evidence in Poland that both the *H. pylori* infection and peptic ulcerations decline in recent years, while the ulcer complications such as hemorrhages and perforations remain at the same level possibly due to increased use of NSAID and the occurrence of idiopathic ulcers.

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